UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

06/25/2001
MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: Health Effects Division Toxicity Chapter for Disulfoton for Reregistration Eligibility Decision (RED)(Reformatted and Revised).

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INTRODUCTION:

This Toxicology Chapter for the Reregistration Eligibility Decision Document represents the second revision to the Toxicology Chapter. The chapter is reformatted according to the SOP as of June 21, 2000. The chapter incorporates two new dermal toxicity studies and a 3rd HIARC report with revisions to the Occupational/residential exposure endpoints only.

EXECUTIVE SUMMARY:

Disulfoton was too toxic for guideline studies on primary eye, skin irritation and dermal sensitization to be conducted, thus the data requirements were waived. Disulfoton is classified as acutely toxic, toxicity category I, by the oral, dermal and inhalation routes of exposure.

The mode of action of disulfoton is inhibition of cholinesterase. In all of the studies evaluated in this hazard assessment, the LOAEL and NOAEL were established through the inhibition of cholinesterase (the basis for all regulatory endpoints). Clinical signs, such as muscle fasciculation and tremors are seen either at higher dose levels or at the LOAEL for some studies. All three cholinesterases (plasma, erythrocyte and brain) are inhibited at the lowest dose tested and

are likely to occur across species including humans. There are slight species differences, but the differences may be due to normal variation and differences in the duration of the studies conducted in different species. Adult females appear to be slightly more sensitive, and in a 6-month study in rats (MRID# 43058401), cholinesterase inhibition was seen only in females.

The cholinesterase NOAELs ranged over a 10 fold exposure levels between acute and chronic studies in rats. Longer exposure always show cholinesterase inhibition at lower dose levels. Clinical signs occurred at the same dose level as cholinesterase inhibition in the acute neurotoxicity study, whereas in the 90-day neurotoxicity study, cholinesterase inhibition occurred at a lower dose level. Motor activity was affected at lower dose levels in the 90-day study than in the acute study, but no treatment related or significant neuropathology occurred either acutely or in the 90-day studies. No organophosphate induced neuropathy (OPIDN) or inhibition of the neurotoxic target enzyme (NTE) was seen in the acute delayed neurotoxicity study.

There is no increased susceptibility to fetuses or pups in acceptable developmental and reproductive toxicity studies in the rabbit or rat. Pup death occurred at the highest dose tested. The deaths were attributed to an inadequate milk supply and maternal care failure. In the developmental toxicity study in the rat, developmental toxicity occurred at higher doses than caused toxicity in dams. Developmental toxicity in the rat was seen in the form of incomplete ossification, but no developmental toxicity was seen in the rabbit at the dose levels administered. In the study on reproduction, cholinesterase was inhibited (plasma, erythrocyte and brain) in parents at lower dose levels than in pups.

No obvious endocrine disruption was seen in any of the studies. Absolute testes and ovarian weights were decreased at the highest dose level, which may be endocrine mediated. These organ weight decreases occurred in the presence of relatively severe cholinesterase inhibition. However, the effect on organ weights could not be unequivocally attributed to endocrine effects.

There is an adequate dermal absorption study in rats and adequate 3-day dermal rat study and 21-day dermal studies in rabbits showing cholinesterase inhibition (plasma, erythrocyte and brain).

There are no carcinogenicity concerns in two acceptable studies in the rat and mouse. An adequate dose level was reached in the study in rats to test the carcinogenic potential of disulfoton, based on decreased body weights and body weight gains. In mice, the highest dose tested in this study is approximates 35% of the LD_{50} and higher dietary concentrations would have resulted in significant compound-related mortality of the test animals. Thus, the dose levels were considered adequate to test the carcinogen potential of disulfoton in mice.

Disulfoton is positive in some mutagenicity studies without activation, but negative or weakly positive in most with activation. With no carcinogenicity concerns and no reproductive toxicity concerns at relevant dose levels, the mutagenicity concerns are low. The mutagenicity data base is complete for the pre-1990 required three mutagenicity categories and the *in vivo* data base support a lack of concern for the mutagenicity of disulfoton.

The metabolism of disulfoton was studied in the rat. The toxic metabolites of disulfoton are disulfoton sulfoxide, disulfoton sulfone, disulfoton oxygen analog (demeton-S), disulfoton oxygen analog sulfoxide and disulfoton oxygen analog sulfone. Disulfoton was found to be rapidly absorbed and excreted with over 95% of the administered C^{14} labeled disulfoton being recovered in the urine and approximately 90% excretion within 24 hours. Less than 2% was recovered from the feces. Bioaccummulation was not observed with less than 0.3% being recovered in tissues and less than 1% being recovered in the carcass. A major metabolite was incompletely identified, but it co-

chromatographed with 1-(ethylsulfonyl)-2-(methylsulfonyl)ethane, a fully oxidized form of the putative hydrolysis product.

The Metabolism Committee determined that the raw agriculture commodity, meat, diary and poultry product residues to be regulated are disulfoton, disulfoton oxygenated analog and their sulfoxides and sulfones.

DISULFOTON

PC Code: 032501

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

Date completed

Prepared for:
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form: FINAL June 21, 2000

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Registration Action Branch-3 (7509C)

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1.0 HAZARD CHARACTERIZATION

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The Metabolism Committee determined that the raw agriculture commodity, meat, diary and poultry product residues to be regulated are disulfoton, disulfoton oxygenated analog and their sulfoxides and sulfones.

2.0 REQUIREMENTS

The requirement (CFR 158.340) for food and non food use for disulfoton are in Table 1. Use of guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test		Technical	
		Required	**Satisfied**
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	Yes	Yes[1]
870.3150	Oral Subchronic (nonrodent)	Yes	Yes[2]
870.3200	21-Day Dermal	Yes	Yes
870.3250	90-Day Dermal	No	Yes
870.3465	90-Day Inhalation	Yes	Yes
870.3700a	Developmental Toxicity (rodent)	Yes	Yes
870.3700b	Developmental Toxicity (nonrodent)	Yes	Yes
870.3800	Reproduction	Yes	Yes
870.4100a	Chronic Toxicity (rodent)	Yes	Yes
870.4100b	Chronic Toxicity (nonrodent)	Yes	Yes
870.4200a	Oncogenicity (rat)	Yes	Yes
870.4200b	Oncogenicity (mouse)	Yes	Yes
870.4300	Chronic/Oncogenicity		
870.5100	Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300	Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	Yes	Yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	Yes	Yes

Test	Technical	
	Required	**Satisfied**
870.6100a Acute Delayed Neurotox. (hen)	Yes	Yes
870.6100b 90-Day Neurotoxicity (hen)	No	-[3]
870.6200a Acute Neurotox. Screening Battery (rat)	Yes	Yes
870.6200b 90 Day Neuro. Screening Battery (rat)	Yes	Yes
870.6300 Develop. Neuro	Yes	Pending[4]
870.7485 General Metabolism	Yes	Yes
870.7600 Dermal Penetration	Yes	Yes
Special Studies for Ocular Effects		
Acute Oral (rat)	Reserved	No
Subchronic Oral (rat)	Reserved	No
Six-month Oral (dog)	Reserved	No
Special Studies (NG)		
Acute and 3-5 day Inhalation (rat)	No	Yes[5]
3-Day Dermal (rat)	No	Yes[5]
6-Month Cholinesterase (rat)	Yes	Yes[6]

[1] Requirement is satisfied by Guideline 870.4100a; [2] Requirement is satisfied by Guideline 870.4100b; [3] Not required when the 870.6200a is negative. [4] Currently being conducted in response to the general data-call-in for organophosphates. [5] Special studies used in the assessment of occupational/residential exposure. [6] Requested special study for assessment purposes.

3.0 DATA GAP(S)

There are no data gaps, however, disulfoton is subject to a data-call-in for organophosphate pesticides (a confirmatory developmental neurotoxicity study).

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Disulfoton is acutely toxic (Toxicity category I) with an oral LD50 of 1.9 mg/kg for female rats. The dermal LD50 is 3.6 mg/kg for female rats. Note at the LD50, apparently greater than 50% of dermaly applied disulfoton is absorbed, while at lower concentrations only 36% is absorbed. The data requirements for primary eye irritation, dermal irritation and dermal sensitization were waived because of the acute toxicity of disulfoton. The studies on acute neurotoxicity in the hen and rat showed cholinesterase inhibition, but no neuropathy. The acute toxicity data on disulfoton technical are summarized below in Table 2.

Table 2. Acute Toxicity Data on disulfoton

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral	00139595,Doc# 003958,p41	LD_{50} = M: 6.2 mg/kg; F:1.9 mg/kg	I
870.1200	Acute Dermal	Acc# 07793, Doc# 03958,p71 & 004223,p24	LD_{50} = M: 15.9 mg/kg; F: 3.6 mg/kg	I
870.1300	Acute Inhalation	00147754, Doc# 05789	LC_{50} = M: 0.06 mg/L; F: 0.015 mg/L	I
870.2400	Primary Eye Irritation	Data requirement waived. Doc# 03958,p12; 004223,p14	Defaults to most severe category	
870.2500	Primary Skin Irritation	Data requirement waived. Doc# 03958,p12;004223.p14	Defaults to most severe category	
870.2600	Dermal Sensitization	Data requirement waived. Doc# 03958, p12	Defaults to most severe category	

4.2 Subchronic Toxicity

Chronic feeding toxicity studies in the dog, rat and mouse satisfy this requirement for oral subchronic studies. The toxicity data base for subchronic toxicity is considered complete. No additional studies are require at this time.

Subchronic inhalation studies in the rat and dermal studies in the rabbit show that cholinesterase is inhibited at the LOAEL. Almost all the studies showed cholinesterase was inhibited in all three compartments.

In addition, subchronic oral neurotoxicity studies in the rat (See Section 4.10) and special 3-day dermal studies in the rat (See Section 4.7) show that cholinesterase is inhibited at the LOAEL.

870.3200 21-Day Dermal Toxicity - Rabbits (82-5)

CITATION: Flucke, W. (1986) Study of Subacute Dermal Toxicity to Rabbits. Bayer AG, Fachbereich Toxikologie, Wuppertal - Elberfeld, F.R. Germany. Study No.:14747. June 20, 1986. MRID 00162338. Unpublished.

EXECUTIVE SUMMARY: In a study (MRID 00162338) S276 Technical disulfoton (97.8% a.i., Batch No. 79-R-225-40), was applied to the shaved skin of 5 New Zealand White rabbits/sex/dose at dose levels of 0, 0.4, 1.6 or 6.5 mg/kg, 6 hours a day, 5 days/week for 15 days. Doses were selected based on a preliminary range-finding study in which clinical signs of cholinergic intoxication and death at 10 mg/kg/day following 1 or 2 applications. Slight inhibition of plasma

ChE at 2 mg/kg and no effect on plasma or RBC ChE inhibition at 0.4 mg/kg. Plasma and RBC ChE were measured at study initiation, day 6, 11, and termination. Brain ChE was determined at termination.

Repeated dermal application of disulfoton or vehicle (Cremophor EL in sterile saline) 6 hours a day for 15 days had no effect on hematology, clinical chemistry, urinalysis, gross pathology and absolute and relative organ weights. There was no dermal reaction to repeated dermal application. **Systemic Toxicity** was observed in high-dose males and females as a marked reduction in food consumption and body weights and death ensuing within 1 to 2 weeks of initiation of treatment. The **Systemic Toxicity NOAEL = 1.6 mg/kg/day** and **LOAEL = 6.5 mg/kg/day**, based on reduced food consumption and weight gain.

At the highest dose, all males and females died or were sacrificed following ≈ 6 days of treatment due to acute cholinergic signs such as muscle spasms, dyspnea and salivation. In one high dose male which survived 6 treatments, plasma (75%) and RBC (31%) Cholinesterase was depressed. Plasma ChE of mid-dose males (17 - 24%) and females (31 - 44%) depressed; RBC ChE of males (15 - 19%) and females (7 - 33%) was depressed, compared to concurrent controls. Brain ChE of males and females was depressed 7 - 8%. The ChE **NOAEL = 0.4 mg/kg/day and LOAEL = 1.6 mg/kg/day**, based on inhibition of plasma and RBC ChE and marginal inhibition of brain ChE.

The study is classified as **Acceptable** and satisfies the guideline requirement for a subchronic dermal toxicity study (82-2) in rabbits.

870.3200 21-Day Dermal Toxicity - Rabbit

CITATION: Flucke, W (1988) S 276 Technical grade Disulfoton: Study of the Subacute Dermal Toxicity to Rabbits. Bayer AG., Germany. Study Number 98347. Report No. 116342, January 5, 1988. MRID 45239601. Unpublished.

SPONSOR: Bayer Corporation, Stillwell, KS.

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study in rabbits (MRID 45239601), disulfoton (97% a.i.%) was administered dermally to New Zealand White (HC:NZW) rabbits (5/sex/dose) at dose levels of 0, 0.8, 1.0 or 3.0 mg/kg/day for 21-days. Plasma, erythrocyte cholinesterase was determined day -2, 8, 15 and 21. Brain cholinesterase was determined at termination on day 21. Plasma and erythrocyte cholinesterase were compared with day -2 values while brain cholinesterase was compared with concurrent control values. Clinical observations, chemistry and histological examination of tissues were conducted.

Body weight was slightly decreased and statistically significant (-3% compared with controls) during the last 2 weeks of the study at 3.0 mg/kg/day in females. Clinical signs consistent with cholinergic signs occurred in males at the end of the study. Muscle spasm, tremors, diarrhea, and/or difficulty in breathing in 4 animals and one male death occurred at 3.0 mg/kg/day toward the end of the study. One female was lethargic and had difficulty breathing on the last day of the study at 3.0 mg/kg/day. No differences attributed to treatment were noted in organ weights or clinical

chemistries other than cholinesterase activity.

Plasma cholinesterase was statistically significantly inhibited in males at 1.0 and 3.0 mg/kg/day at day 15 (22%) and 21 (24%) and at day 8 (63%), 15 (70%) and 21 (65%), respectively. In females, plasma cholinesterase was statistically significantly inhibited only at 3.0 mg/kg/day and only on day 15 (61%) and 21 (61%), but it was 44% inhibited on day 8 (not statistically significant). Erythrocyte cholinesterase was statistically significantly inhibited in males days 8 (53%), 15 (56%) and 21 (62%) at 3.0 mg/kg/day and day 21 (17%) at 1.0 mg/kg/day. In females, erythrocyte cholinesterase was statistically significantly inhibited on days 8 (42%), 15 (55%) and 21 (51%) at 3.0 mg/kg/day, but at 1.0 mg/kg/day it was statistically significantly inhibited on days 15 (28%) and 21 (25%) only. Although, erythrocyte cholinesterase was inhibited in females 30% at 1.0 mg/kg/day on day 8, it was not statistically significant, possibly due to the high standard deviation in day -2 values used for comparison. However, concurrent control females and the 0.8 mg/kg/day dose group showed 21% and 24% erythrocyte cholinesterase inhibition on day 8, respectively, compared with the -2 day values. Thus the 30% erythrocyte cholinesterase inhibition in females on day 8 at 1.0 mg/kg/day was not considered biologically significant. At termination, brain cholinesterase was 55% inhibited in males and 27% inhibited in females only at 3.0 mg/kg/day (neither were marked as being statistically significant, but they were depressed according to the report author). Due to the timing of sample collection in females, depression in brain cholinesterase values seen for females, probably had time to partly reverse before collection.

There was no definitive indication from these data that there was or was not accumulation of the test material, which caused increased cholinesterase depression with days on study, however, frequently the day 15 and/or day 21 values were nominally lower than the day 8 cholinesterase activity values, and cholinergic clinical signs occurred in animals after day 15.

The overall NOAEL was 0.8 mg/kg/day for any day of dosing. The overall LOAEL is 1.0 mg/kg/day based on statistically significant inhibition of plasma cholinesterase in males by day 15 and statistically significant inhibition of erythrocyte cholinesterase inhibition in females by day 15. Significant plasma and erythrocyte cholinesterase inhibition occurred by day 8 only at 3.0 mg/kg/day in males and females.

This study is classified **acceptable** and satisfies the Subdivision F guideline requirement for a 21-day dermal study in rabbits (82-2).

870.3465 Subchronic Inhalation/Rats (82-4)

CITATION: Shiotsuka, RN (1989) Subchronic inhalation study of technical grade disulfoton (Di-Syston®) inhalation in rats. Testing Lab: Mobay Corp. Study# 88-141-AU/99648. Date: 7/31/89. MRID# 41224301. Unpublished study.

Executive Summary: Disulfoton was administered by inhalation to 12 Fisher 344 rats per sex per group for air control, polyethylene glycol-400: 50% ethanol vehicle control, 0.015, 0.15 or 1.5 mg/m^3 nominal dose levels for 90-days in a nose only chamber (MRID No.: 41224301). The analytical determined mean dose levels were 0, 0, 0.018, 0.16 and 1.4 mg/m^3 for male and female rats. The rats were exposed to the test material 6 hours per day, 5 days per week. The particle sizes

in the inhalation chambers had a MMAD ± geometric standard deviation of 1.3 ± 1.4, 1.1 ± 1.3, 1.0 ± 1.3 and 1.1 ± 1.4 μm for the two controls, 0.015, 0.15 and 1.5 mg/m^3 nominal dose levels, respectively. The range in mean daily particle sizes had a MMAD of 0.5 ± 1.0 μm to 2.6 ± 1.6 μm.

At the highest dose level, plasma cholinesterase was depressed in males (19% and 14% from air controls at 38 days and term, respectively, $p \leq 0.05$) and in females (27% and 31% from air controls at 38 days and term, respectively, $p \leq 0.05$). Brain cholinesterase was depressed in males (29%) and females (28%) at termination. Erythrocyte cholinesterase was depressed in females at 38 days (11% at 38 days, $p \leq 0.05$, not considered biologically relevant) at 0.16 mg/m^3 and higher in males and females at 1.4 mg/m^3 at 38 days and term. Brain cholinesterase were depressed (10%, $p \leq 0.05$) at 0.16 mg/m^3, but this degree of variation was not considered biologically relevant due to variation noted in this parameter. Inflammation of the male nasal turbinates occurred at 1.4 mg/m^3. No other test material related effects were noted. **The NOAEL/LOAEL is 0.16 mg/m^3/1.4 mg/m^3 or 0.00016/0.0014 mg/L for plasma, erythrocyte and brain cholinesterase depression.**

Core classification: Guideline. The study (MRID# 41224301) is acceptable under guideline 82-4 for a 90-day inhalation study in rats.

Comments about study and/or endpoint: This study also has cholinesterase inhibition data for day 37.

4.3 Prenatal Developmental Toxicity

There is no increased susceptibility to fetuses in acceptable developmental toxicity studies in the rabbit or rat. In the developmental toxicity study in the rat, developmental toxicity occurred at higher doses than caused toxicity in dams. Developmental toxicity in the rat was seen in the form of incomplete ossification, but no developmental toxicity was seen in the rabbit at the dose levels administered.

870.3700 Prenatal Developmental Toxicity Study in Rats (83-3)

CITATION: Lamb-DW and Hixson-EJ (1983) Embyrotoxic and teratogenic effects of Disulfoton. Study# 81-611-02 submitted by Mobay Chem. Corp. May 13, 1983. MRID#: 00129458. Unpublished Report.

EXECUTIVE SUMMARY: Disulfoton, technical (98.2%) was administered in a carbowax (polyethylene glycol 400) vehicle by gavage to 25 pregnant Sprague Dawley rats/group at 0, 0.1, 0.3 or 1.0 mg/kg/day from day 6 through day 15 of gestation (MRID# 00129458). On day 21, the rats were killed and 50% of each litter was examined for skeletal anomalies and the remainder for visceral anomalies. Cholinesterase inhibition studies on the dams at 21 days (2 weeks dosing) indicated an NOAEL/LOAEL of 0.1/0.3 mg/kg/day based on 41% inhibition of both plasma and erythrocyte cholinesterase. Fetuses showed incomplete ossification of the intraparietals and sternebrae at 1.0 mg/kg/day.

The NOAEL/LOAEL for maternal toxicity were 0.1/0.3 mg/kg/day based on 41% inhibition of both plasma and erythrocyte cholinesterase. The NOAEL/LOAEL for

developmental toxicity were 0.3/1.0 mg/kg/day based on incomplete ossification of the intraparietals and sternebrae.

The study is acceptable under Guideline 83-3 for a developmental toxicity study in rats.

870.3700 Prenatal Developmental Toxicity in Rabbits (83-3)

CITATION: Tesh-JM et al. (1982) S276: Effects of oral administration upon pregnancy in the rabbit. An unpublished report (Bayer No. R 2351) prepared by Life Science Research, Essex, England and submitted to Bayer AG, Wuppertal, Germany. Dated December 22, 1982. MRID# 00147886. Unpublished Report.

EXECUTIVE SUMMARY: Disulfoton, technical was administered by gavage in a corn oil vehicle (5ml/kg) to 15, 14, 14 or 22 pregnant New Zealand White rabbits per group at 0, 0.3, 1.0 or 3.0 mg/kg/day, respectively from day 6 to 18 of gestation (MRID# 00147886). Since mortality and clinical signs were observed at 3.0 mg/kg/day, this dose level was reduced to 2.0 mg/kg/day and finally to 1.5 mg/kg/day. Analysis showed that the dosing solutions were 17, 14 and 10% below the target concentrations for the low to highest doe tested (HDT), respectively. Females were artificially inseminated.

Maternal signs such as muscle tremors, unsteadiness/ in coordination and increased respiratory rate were seen 4 hours after dosing and in some cases persisted for more than 24 hours at the HDT. No toxic signs were noted at the MDT and LDT. At the MDT one low and 3 control females were found dead or moribund from a mid-ear disease or respiratory infection. Test material related mortalities at the HDT occurred mostly prior to dosage reduction to 1.5 mg/kg. Nine of 22 animals survived to termination at the HDT. Two animals aborted at the MDT. No test material related body weight changes were noted.

No dose related soft tissue or skeletal anomalies were noted at any dose levels.

The NOAEL/LOAEL for dams were 1.0/1.5 based on tremors, unsteadiness/in coordination and increased respiration. The NOAEL/LOAEL for developmental toxicity were >3.0/>3.0 mg/kg/day.

The study is acceptable for Guideline 83-3 for a developmental toxicity study in rabbits and was upgraded from supplementary to fully acceptable in HED Doc# 004698 and by the RfD/QA Peer Review Committee.

4.4 Reproductive Toxicity

There is no increased susceptibility to pups in two acceptable reproductive toxicity studies in the rat. Pup death occurred in the newer study at the highest dose tested. The deaths were attributed to an inadequate milk supply and maternal care failure. In the newer study on reproduction, cholinesterase was inhibited (plasma, erythrocyte and brain) in parents at lower dose levels than in pups. The newer study measured more endpoints than the older study, but the results of the two studies were not inconsistent.

870.3800 Two-Generation Reproductive Toxicity Study/Rats (83-4)

CITATION: Astroff, A Barry (1997) A Two Generation Reproductive Toxicity study with Disulfoton Technical (Disyston ®) in the Sprague Dawley Rat. Laboratory name Bayer Corp.,

Stilwell, KA. Laboratory report number: 95-672-FZ, report# 108002, File 8368. November 19, 1997. MRID# 44440801. Unpublished

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID# 44440801) disulfoton, technical, 99% a.i.] was administered to 30 Sprague Dawley rats/sex/dose in the diet at dose levels of 0, 0.5, 2.0 or 9.0 ppm (0, 0.025, 0.10 or 0.45 mg/kg/day by std. tables). Dosing was continuous for the P0 and F1 generation. Only one littering/animal/group was conducted. In this second 2-generation reproductive toxicity study with disulfoton, cholinesterase activity was measured in adults during pre-mating (at 8 weeks) and at termination and in pups at postnatal day 4 and day 21 in the 2 generations.

The major effects noted were cholinesterase inhibition and dams with no milk. In P0 males, plasma cholinesterase (PCHE) was significantly depressed and dose related pre-mating at 9.0 ppm (≥-34%) and at termination at 2.0 (≥-11%) and 9.0 ppm (-46%). In P0 females, plasma cholinesterase (PCHE) was significantly depressed pre-mating (≥-29%) and at termination (≥-52%) at ≥2.0 ppm. In P0 males and females erythrocyte cholinesterase (ECHE) was significantly depressed and dose related at ≥2.0 ppm (≥-38% & ≥-35% males and ≥-46% & ≥-80% females) a pre-mating and termination, respectively, but only in females at termination (≥-14%) at ≥0.5 ppm. In P0 males and females brain cholinesterase (BCHE) was significantly depressed and dose related at ≥2.0 ppm in males (≥-11%) and ≥-14% in females at ≥0.5 ppm.. PCHE and ECHE depression in F1 males and females followed a similar nominal pattern to that in P0 males and females, except that the statistical significance varied within the F1 between two dose levels; sometimes the dose level showing statistical significance was higher and sometime lower of the two. In F1 males and females, BCHE was significantly depressed and dose related at ≥2.0 ppm in males (≥-14%) and in females (≥-50%). In F1 and F2 male and female pups at day 4 and/or day 21 of lactation, PCHE and ECHE were significantly depressed at 9.0 ppm. Values for PCHE and ECHE, respectively were at day 4 or day 21 in F1 male pups were (-24% & -47%) and for F1 female pups (-31% & -43%). Values for PCHE and ECHE, respectively, were at day 4 or day 21 in F2 male pups were (-46% & -53%) and for F2 female pups (-48% & -51%). In F1 and F2 male and female pups BCHE was significantly depressed at day 4 and day 21 at 9.0 ppm only (day 4 = -14% F1 males and -17% F1 females)(day 21 = -19% F1 males and -23% F1 females)(day 4 = -11% F2 males and -13% F2 females)(day 21 = -35% F2 males and -37% F2 females).

Muscle fasciculation (1 P0 female), tremors (15 P0 females, 10 F1 females) and dams (7 F1 dams) with no milk were noted at 9.0 ppm. No treatment related organ weight changes or histopathology were noted in P0 or F1 males or females at any dose level.

Clinical observations indicate that dams were not caring for their pups. Observed affects in pups in the 9.0 ppm group included 12 F1 (2 dams) pups cold to the touch and 3 F1 (2 dams) not being cared for and 63 F2 pups (7 dams) with no milk in their stomachs and 93 F2 weak pups (10 dams) from the affected dams. In addition, 1 P0 dam was salivating and gasping and did care for the litter and the litter died at 2.0 ppm. This effect at 2.0 ppm was considered test material related by the summary author of the 6(a)(2) submission (See summary 6(a)(2) report, MRID# 44440801; memorandum from David Anderson to PM 53, dated March 24, 1998, D242573), but ignored in the final report summary. Findings at necropsy were noted in F2 pups at 9.0 ppm that were expected in view of the maternal toxicity at this dose level. The report reasonably considered the pup deaths due to failure of maternal care, because of the weak and cold to the touch pups and failure of the pups to show milk in their stomachs. On careful examination of the report, this reviewer agrees

with this conclusion. Thus, under these conditions, the effects in pups were caused by maternal toxicity and not the direct toxicity of disulfoton on pups.

Body weight change was lower than control values during gestation in P0 (-9%) and F1 (-15%) females. Body weights were significantly reduced at termination from control values in P0 (-6%) and F1 females (-13%) and in F1 males (-8%). No other significant body weights or changes were noted.

The P0 parental LOAELs were 0.5 ppm (0.025 mg/kg/day) based on brain cholinesterase activity depression in P0 females with tremors and muscle fasciculation at 9 ppm in females during gestation and lactation from both generations and with body weight decrements at 9.0 ppm, especially at termination. A NOAEL of 0.5 ppm (0.025 mg/kg/day) was seen in F1 parents. F1 and F2 pup (4 day and 21 day old) cholinesterase activity, including brain cholinesterase activity was depressed only at 9.0 ppm (0.45 mg/kg/day) with 2.0 ppm (0.10 mg/kg/day) being the NOAEL. The F1 pup NOAEL/LOAEL were 2.0/9.0 ppm (0.10/0.45 mg/kg/day) based on treatment related pup deaths and pup weight decrements at 9.0 ppm, probably from inadequate maternal care.

The reproductive study in the rat is classified acceptable and does satisfy the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4) in rat.

870.3800 Two-Generation Reproductive Toxicity/Rats (83-4)

CITATION: Hixson, EJ and Hathaway, TR (1986) Effect of disulfoton (Di-Syston®) on reproduction in the rat. Conducting laboratory: Mobay Chem. Date: 2/12/86. Study# 82-671-02. MRID# 00157511. Unpublished Study.

EXECUTIVE SUMMARY: In an acceptable 2-generation reproductive toxicity study (MRID# 00157511; HED Doc# 011959 & 005796), disulfoton, technical (97.8%) was administered at 0, 1, 3 or 9.0 ppm (0, 0.04, 0.12 or 0.36 mg/kg/day). In this first and older reproduction study cholinesterase activity was measured in pups, but not in adults. In this first study of reproductive toxicity, the parental toxicity NOAEL/LOAEL were 3/9 ppm or 0.12/0.36 mg/kg/day based on nominally reduced incidence of females with sperm and reduced body weight in gestating and lactating P0 females with cholinesterase being probably inhibited with a NOAEL/LOAEL of 1/3 ppm or 0.04/0.12 mg/kg/day. These latter cholinesterase results were supported by results from the chronic/oncogenicity rat study. Toxicity on reproduction showed a NOAEL/LOAEL of 1/3 ppm or 0.04/0.12 mg/kg/day based on F1a weanling pup brain cholinesterase inhibition and F2b pup survival.
The study is acceptable for a guideline (83-4) study on reproduction in the rat.

4.5 Chronic Toxicity

Two chronic feeding studies were conducted in dogs, both showing cholinesterase inhibition at the LOAEL. The newer study in dogs included cholinesterase inhibition in eye tissue and studied more parameters and showed a slightly lower NOAEL than the older study, but the studies were

consistent with the each other. The newer study was used for risk assessment. The chronic feeding toxicity study in the rodent is satisfied by the combinded chronic/carcinogenicity study in rats (See Section 4.7).

870.4100b Chronic Toxicity - Dogs (83-1b)

CITATION: Jones, R.D. and T.F. Hastings (1997) Technical grade Disulfoton: A chronic toxicity feeding study in the Beagle dog. Bayer Corporation, Stillwell, KS. Study Number 94-276-XZ. Report No. 107499. February 5, 1997. MRID 44248002. Unpublished.

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 44248002), disulfoton (97% a.i.%) was administered orally in the diet to purebred beagle dogs (4/sex/dose) at dose levels of 0.5, 4 or 12 ppm (equivalent to 0.015, 0.121 and 0.321 mg/kg/day for males; and 0.013, 0.094 and 0.283 mg/kg/day for females) for one year. Potential ocular and neurologic effects were addressed.

Plasma cholinesterase was decreased starting at day 7 in the 4.0 ppm dose groups of the study through to termination (males 39% to 46%; females 32% to 45%). Erythrocyte cholinesterase was decreased starting at day 91 in the 4.0 ppm dose groups through to termination (males 23% to 48%; females 17% to 49%). Not all the values at 4.0 ppm were statistically significant, probably because of the wide range in values, but at least 2 animals per group showed biologically significant cholinesterase inhibition.

By termination cholinergic effects of the plasma, erythrocytes, brain, and ocular tissues were observed in both sexes in the 4 and 12 ppm treatment groups. Plasma and erythrocyte cholinesterase depression are compared to pretreatment values. Brain, cornea, retina and ciliary body cholinesterase depression are compared with concurrent control values at termination only. In the 12 ppm treatment groups, depressed cholinesterase was observed in plasma (56%-63%), erythrocytes (30%-91%), and brain (32%-33%) compared to their respective controls. In the 4 ppm treatment groups in males and females, cholinesterase was depressed in plasma (38%-46%), erythrocytes (40%- 38%), and brain (females only, 22%). Disulfoton inhibited cholinesterase of the cornea, retina, and ciliary body, but did not appear to alter the physiologic function of the visual system. In the 12 ppm treatment groups, depressed cholinesterase was observed in the cornea (60-67%), ciliary body (45-54%), and retina (males only; 67%). In the 4 ppm treatment groups, cholinesterase was inhibited in the cornea (50-60% lower), and retina (females only, 25%). No treatment-related ophthalmology findings or histological or electrophysiological changes in the retina were observed. No other treatment-related effects were observed. No animals died during the study. No treatment-related effects were observed in systemic toxicity including food consumption, body weights, clinical signs, hematology, clinical blood chemistry or urinalysis parameters, electroretinograms, electrocardiogram or clinical neurological findings, organ weights or gross or microscopic post-mortem changes in any treatment group. No neoplastic tissue was observed in dogs in the treatment and control groups. **The LOAEL is 4 ppm (0.094 mg/kg/day), based on depressed plasma, erythrocyte, and corneal cholinesterase levels in both sexes, and depressed brain and retinal cholinesterase levels in females. The NOAEL is 0.5 ppm (0.013 mg/kg/day). These LOAEL/NOAEL for plasma cholinesterase inhibition extend from day 7 to termination and for erythrocyte cholinesterase inhibition they extend from day 91 to**

termination.

This study is classified **acceptable** and satisfies the Subdivision F guideline requirement for a chronic oral study in non-rodents (83-1b).

870.4100b Chronic Toxicity - Dogs (83-1b)

CITATION: Hoffman, K.; Weischer, C.H.; Luchaus, G.; et al. (1975) S 276 (Disulfoton) Chronic Toxicity Study in Dogs (Two-year Feeding Experiment). Bayer, AG, W. Germany. Report No. 45287. December 15, 1976. MRID 00073348. Unpublished.

EXECUTIVE SUMMARY: In a chronic feeding study (MRID 00073348) Technical Di-Syston (95.7% a.i.) was administered in diet to 4 Beagles/sex/dose in the diet at dose levels of 0, 0.5, 1 or 2/5/8 ppm (0, 0.0125, 0.025 or 0.05/0.125/0.2 mg/kg/day, converted) for 104 weeks. In the high-dose group, 2 ppm was given for first 69 weeks, 5 ppm from 70 - 72 weeks, and 8 ppm from week 73 - termination. Body weights were determined weekly for 52 weeks, then biweekly until termination. Clinical evaluations to detect cholinergic signs, ophthalmological evaluations, hematology, clinical chemistries, urinalysis were performed on all animals pre-treatment, on weeks 13, 26, 39, 52, 65, 78, 91, and at termination. Plasma, and RBC cholinesterase was determined at 2-week intervals during the first 13 weeks and at about 3 month intervals thereafter. Brain cholinesterase was determined immediately after necropsy.

Treatment had no effects on general appearance and behavior, and toxic signs, ophthalmoscopy examinations, food consumption, body weight, hematology, clinical chemistry, organ weight and/or histopathology. At 2 ppm, plasma and RBC cholinesterase (ChE) was inhibited 50 and 33% in males and 22 and 36% in females, respectively, during week 40. Large fluctuations in plasma and RBC ChE inhibitions occurred until the dose was raised to 8 ppm. By the termination (104 weeks) of study, the plasma, RBC and brain ChE was inhibited 65, 58, and 34% in males and 49, 48 and 18% in females, respectively, compared to pre-treatment values. Based on the above, the **Systemic Toxicity NOAEL = 2 ppm** (0.05 mg/kg/day) and **LOAEL > 2 ppm**. The **cholinesterase NOAEL = 1 ppm** (0.025 mg/kg/day) and **LOAEL = 2 ppm** (0.05 mg/kg/day), based on plasma and RBC ChE inhibition.

The study is classified as **Acceptable** and **satisfies** the guideline requirement for a chronic toxicity study (83-1b) in the dog.

4.6 Carcinogenicity

The two carcinogenicity studies in mice and rats were adequately conducted and showed no treatment related carcinogenicity. The study in mice showed only cholinesterase inhibition, but the rat study showed body weight decrement, Harderian gland degeneration, and lesions of the eye and optical nerve, all at higher dose levels than the cholinesterase inhibition.

870.4200b Carcinogenicity/Mice (83-2b)

CITATION: Hayes, R.H (1983) Oncogenicity study of disulfoton technical on mice. Corporate Toxicology Department, Mobay Chemical Corporation, Stilwell, KS. Study No. 80-271-04. August 10, 1983. MRID 00129456. Unpublished study.

EXECUTIVE SUMMARY: In a carcinogenicity toxicity study (MRID 00129456 & 00139598), disulfoton (98.2% a.i.) was administered to 50 Crl:CD-1 mice/sex/dose in the diet at dose levels of 0, 1, 4, or 16 ppm (0.15, 0.6, or 2.4 mg/kg/day, converted) for 108 weeks. In addition, 10 mice/sex/group were used as replacement animals. Cholinesterase activity in the plasma, RBC, and brain was determined at final sacrifice for 10 mice/sex randomly selected from the control and 16 ppm groups.

Treatment had no effect on bodyweights, food consumption, hematology, and mortality. Eight mice i.e., 1 male and 3 females from the 1 ppm group, 3 males from the 4 ppm group, and one male from the 16 ppm group, died during the first month and were replaced. Survival at 18 months ranged from 76 - 86% in all males, and 68 - 82% in all females. At termination survival ranged from 56 - 66% and 38 - 54%, in males and females, respectively. Cholinesterase (ChE) was markedly inhibited at the high-dose. In males, the plasma, RBC and brain ChE was inhibited 79, 56, and 44%; and in females it was inhibited 82, 50, and 46%, respectively, compared to controls. Enlarged spleen, liver, and lymph nodes were observed with greater frequency in females than males,; histologically diagnosed as lymphomas. The number of animals with malignant lymphoma, of all histologic cell types, were 10, 9, 12, and 15 in males and 27, 22, 26, and 34 in females, at 0, 1, 4, and 16 ppm, respectively. Tumor incidence lacked statistical significance by either the Chi-square or Fisher exact test. In high-dose females, absolute and relative kidney weights increased 22% and 11%, respectively, probably related to increased incidence of lymphomas in this organ. None of the increased organ weights/histopathological findings were considered treatment-related.

Based the above findings, the **Systemic Toxicity LOAEL > 2.4 mg/kg/day and LOAEL = 2.4 mg/kg/day**, based on plasma, RBC and brain ChE inhibition in males and females. **The NOAEL = 0.6 mg/kg/day**.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate for testing the carcinogenic potential of disulfoton, even though, there was no clear indications of systemic toxicity such as body weight gains and liver specific enzymes. The highest dose tested in this study is approximates 35% of the LD_{50} and higher dietary concentrations would have resulted in significant compound-related mortality of the test animals.

The study is classified as **Acceptable**, and satisfies the guideline requirement for a oncogenicity study (83-2b) in mice.

4.7 Combined Chronic/Carcinogenicity

870.4300 Combined Chronic/Carcinogenicity - Rats

CITATION : Hayes, R.H (1985) Chronic feeding/oncogenicity study of technical disulfoton (Di-SYSTON) with rats. Mobay Chemical Corporation, Stilwell, KS. Study No. 82-271-01. June 25, 1985. MRID #s 00146873. Unpublished.

and

Supplementary data upgrading MRID# 00146873 from supplementary to acceptable on the Harderian gland (MRID# 41850001) and optical and optic nerve lesions (MRID# 41850002).

EXECUTIVE SUMMARY: In a chronic feeding/carcinogenicity study (MRID # 00146873, 41850001, 41850002) Disulfoton (98.1% a.i., Batch No. 79-R-255-40) was administered to 60 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 0.8, 3.3, or 13 ppm (0, 0.04, 0.165, or 0.650 mg/kg/day, converted by std. tables) for 105 weeks. Hematological determinations were done on 20/sex/dose and urine and blood chemistry on 10/sex/dose, randomly selected, at 0, 3, 6, 12, 18, and 24 months. Plasma and red cell cholinesterase (ChE) was determined on 10 rats/sex/dose at pre-treatment, 4, 14, 27, 53, 79 and 105 weeks and brain ChE at termination.

Administration of disulfoton in the diet up to 13 ppm had no effect on mortality, hematology, clinical chemistry and urine analysis. Mean body weights of high-dose rats were significantly depressed throughout the study. Body weight gains of high-dose males and females were depressed 29% and 48%, respectively, by termination when compared to the controls. At the mid and low dose, mean body weights of males were sporadically depressed, however, by the end of study the mean body weights were similar to controls. Females body weights were not effected at these dose levels. At 13 ppm, in females the absolute heart (9%) , liver (17%), and testes (24%) were decreased; in females the heart (13%), kidneys (13%), liver (27%) and ovaries (57%) decreased. Absolute brain weight was unchanged in males and females. In high-dose females the relative brain (59%), heart (33%), and kidneys (34%) increased, compared to the controls. Also, the relative lung (72%) and liver (9%) and brain (58%) weights were increased. At this dose the male relative brain weights were increased by 17%. None of the aforementioned organ weights were associated with any histopathology corroborative of toxicity. In high-dose males Harderian gland degenerative changes increased to 460% of controls and in females the elevation was dose-related (800, 1100 and 1633% of control values, respectively, all $p \leq 0.05$). Since there is no Harderian gland in the humans, the significance of pathological changes seen in the rat are uncertain. In addition, corneal vascularity (693% of control), corneal epithelial hyperplasia (1633% of control) and optic nerve degeneration (145% of control) were elevated in high-dose females and corneal vascularity (329% of control) in males. The eye histopathology was not affected in the mid and low doses. Based on the above, the **Systemic Toxicity NOAEL = 0.8 ppm (0.04 mg/kg/day) and LOAEL = 3.3 ppm (0.165 mg/kg/day)**, based on Harderian gland degeneration.

At termination, a dose-related inhibition in plasma, red cell and brain ChE was observed at all doses in both sexes. In males the plasma, red cell and brain ChE was inhibited 11%-94%, 19%-80%, and 16%-79%; and in females, it was 25%-95%, 12%-76%, and 21%-82%, respectively, compared to the controls. The **Cholinesterase NOAEL < 0.8 ppm (0.04 mg/kg/day) and LOAEL = 0.8 ppm (0.04 mg/kg/day)**, based on plasma, red cell and brain ChE inhibition in males and females. Starting at week 4 the LOAEL in plasma ChE inhibition was 4 ppm (0.165 mg/kg/day) in males (27%) and females (64%) with a NOAEL of 1 ppm (0.04 mg/kg/day). Starting at week 4 the LOAEL in erythrocyte ChE inhibition was increased at 1 ppm (0.04 mg/kg/day) (LDT) in males (16%) and females (30%) with no NOAEL.

The maximum tolerated dose (MTD) was reached, based on decreased body weights and body weight gains and is considered adequate to test the carcinogenic potential of Disulfoton. Disulfoton treatment did not alter the spontaneous oncogenicity profile in both males and female Fischer 344 rats under the test conditions. In males and females, leukemia, adrenal cortex adenoma, adrenal pheochromocytoma, pituitary adenoma and carcinoma and thyroid-C cell adenoma was

most frequently observed. Mammary gland fibroadenoma in both sexes, but most frequently in females. Testicular interstitial adenoma in males and stromal polyp of the uterus in females was observed. All these neoplasms were similar in type, time of onset, and incidence in both controls and disulfoton treated animals.

The study is classified as **Acceptable** and **satisfies** the guideline requirement for a chronic feeding/carcinogenicity study (83-5) in the rat.

870.4300 Chronic Feeding/Oncogenicity Study/Rats (83-5)

CITATION: Carpy, S.; Klotzsche, C.; Cerioli, A. (1975) Disulfoton: 2-Year Feeding Study in Rats. Sandoz, Ltd., Switzerland. Report No. 47069. December 15, 1976. MRID 00069966. Unpublished.

EXECUTIVE SUMMARY: In a chronic feeding/carcinogenicity study (MRID 00069966) Technical Di-Syston® (95.7% a.i.) was administered to 60 SPF Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 0.5/5.0, 1.0 or 2.0 ppm (0, 0.0215/0.1900, 0.0456, or 0.0893 mg/kg/day in males and 0, 0.0267/0.1960, 0.0419 or 0.1033, mg/kg/day in females, respectively; calculated) for 104 weeks. The 0.5 ppm dose was fed for 81 weeks, then increased to 2 ppm because of no effects seen at the 1 ppm dose level. The rats in the 2 ppm group were initially maintained at 1.5 ppm for 4 - 5 weeks, then increased to full dose. Body weight, food consumption, food efficiency, hematology, clinical chemistries, and urinalysis were determined. Plasma, red cell and brain cholinesterase was determined from 5 overnight fasted animals/sex/group at termination. Necropsy was done on 10 animals/sex/dose; all others were examined for tumors. Histopathology was done on 5 animals/sex from the control and the 5 ppm group.

Treatment with Di-Syston did not effect, food consumption, body weight gain, hematology, clinical chemistry, and urinalysis. Mortality was high (20 - 37%) in females but lacked the dose response and no clear explanation was offered for cause of death; more than 1/3 of the dead animals autolyzed. At 0.5/5 ppm, in males the absolute/relative liver, spleen and kidney weights increased 12%/8%, 21%/17% and 23%/19%, respectively ($P \leq 0.05$); however, the histopathology of the organs were unremarkable. There was a trend for decreased absolute and relative brain weights in males and increased trend in females. The **Systemic Toxicity LOAEL >1 ppm**.

Cholinesterase levels in plasma, red cells and brain was inhibited in males and females at two higher doses and it was dose-related. At 2 ppm, the plasma, red cell and brain ChE of males was inhibited 14, 9.3, 9%, and in females 22, 13.3 and 17%, respectively, compared to the controls. At the 0.5/5 ppm dose, plasma, red cell and brain ChE of males and females was inhibited 20 - 39.6, 18.3 - 27.1 and 25 - 36%, respectively. ChE levels in the 1 ppm group males and females was not effects. The **ChE NOAEL = 1 ppm and the LOAEL = 2 ppm**, based on decreased plasma, red cell and brain cholinesterase levels.

The study is classified as **Unacceptable** and can not upgraded because multiple deficiencies in the conduct of the study and **does not satisfy** the guideline requirement for chronic toxicity/oncogenicity study (83-5) in the rat.

4.8 Mutagenicity

The following was taken from a document written by Nancy McCarroll for the Hazard Identification Assessment Review Committee proceedings. Combining the acceptable studies with the additional EPA-sponsored studies will satisfy the Pre-1991 mutagenicity initial testing battery guidelines. No further mutagenicity testing has been identified at this time. In addition, disulfoton is not genotoxic *in vivo* or carcinogenic in mice or rats.

In some of the mutagenicity studies, positive effects were seen without activation while negative effects were seen with activation. This may be due to microsomal enzyme metabolism, since pretreatment of rats and mice with phenobarbital reduces toxicity from disulfoton.

Gene Mutation (84-2)

Salmonella typhimurium/Escherichia coli reverse gene mutation plate incorporation assay (Accession No. 00028625; Doc. No. 003958: As part of an Agency sponsored mutagenicity screening battery, disulfoton was negative in all strains up to the HTD (5000 μg/plate +/- S9) in three independent trials.

Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay (MRID# 40638401, Doc# 008394): This unacceptable study is considered to be positive, because the assay was conducted at partially soluble levels(0.1-1.0 μL/ml -S9; 0.7-1.0 μL/ml +S9) and insoluble doses (5-10 μL/ml -S9; 3-10 μL/ml +S9) but not active at soluble concentrations ($\leq$0.06 μL/ml +/-S9). The mutagenic response appeared to be stronger without metabolic (S9) activation .

Chromosome Aberrations (84-2)

Mouse micronucleus test (MRID No. 43615701) No increase over background in micronucleated polychromatic erythrocytes (evidence of cytogenetic damage) of mice treated intra-peritoneally up to MTD levels (8 mg/kg). Lethality and other signs of toxicity, but no bone marrow cytotoxicity was seen.

Other Gene Mutations: (84-2)

Bacterial DNA Damage/Repair: *E. Coli* DNA damage/repair test (Accession# 072293; Doc# 004698): The test is negative up to the HDT (10,000 μg/plate +/- S9.

Mitotic Recombination: *Saccharomyces cerevisiae* D3 mitotic recombination assay (Accession# 00028625; Doc# 003958): Disulfoton (up to 5% +/- S9) was negative at this endpoint in the Agency-sponsored mutagenicity screening battery. The study is currently listed as unacceptable, but should be upgraded to acceptable. Upon further review of the data, it was decided that the reason for rejecting the study (number of replicates/dose not provided) did not interfere with the interpretation of the findings.

Sister Chromatid Exchange: Sister chromatid exchange in CHO cells (MRID# 40945001; Doc#

008394): Positive, dose related effects at 0.013-0.1 μL/ml without S9, but not active in the S9 activated phase of testing up to a level (0.20 μL/ml) causing cell cycle delay.

Sister Chromatid Exchange: Sister chromatid exchange in Chinese hamster V79 cells (Accession# 072293; Doc# 0044223): The test is negative without activation up to the HTD (80 μg/ml). Subsequently tested by the same investigators (Chen et al., 1982; Environ. Mutagen. 4: 621-624) in the presence of exogenous metabolic activation and found to be negative up to the HDT (80 μg/ml).

Unscheduled DNA Synthesis (UDS): UDS in WI-38 human fibroblasts (Accession# 000028625; Doc# 003958): The test is positive in the absence of S9 activation at precipitating doses (1000-4000 μg/ml). With S9 activation, the study was negative at comparable percipitating concentrations.

Other EPA Sponsored Mutagenicity Studies:

Disulfoton was also included in second tier mutagenicity test battery performed at the EPA (EPA-600/1-84-003) in 1984. Although DERs have not been prepared for these additional assays, we assess that they are acceptable for regulatory purposes.

Mouse Lymphoma L5178Y TK+/- forward gene mutation assay: The test was positive in the absence of S9 activation with concentration dependent and reproducible increases in mutation frequency at 40-90 μg/ml; higher dose levels were cytotoxic. No mutagenic activity was seen in the presence of S9 activation up to a cytotoxic dose (150 μg/ml).

Mouse Micronucleus Assay: The test is negative in Swiss Webster mice up to a lethal dose (8 mg/kg) administered once daily for 2 consecutive days by intra-peritoneal injection. No bone marrow cytotoxicity was seen.

Sister Chromatid Exchange in CHO cell assay: The non-activated test was negative up to levels ($\geq$0.02%) that caused cell cycle delay, but the test material was weakly positive at a single dose (0.04%) with metabolic activation.

4.9 Neurotoxicity

The neurotoxicity studies conducted on disulfoton showed cholinesterase inhibition and effects associated with cholinesterase inhibition, but no neuropathy in the hen or the rat studies.

870.6100 Acute Delayed Neurotoxicity - Hen

CITATION: Andrews, P and Popp, A (1999) S S276(c.n.: Disulfoton) Study for Delayed neurotoxicity following Acute Oral Administration to Hens, EPA Guideline 81-7, Bayer Report No. 109423. 75 pages. November 5, 1999. MRID 44996401. Unpublished.

SPONSOR: Bayer Corp., Agriculture Division, 8400 Hawthorn Road, Kansas City, MO 64120-

0013. Telephone: 816-242-2000. Dr. Premjit Halarnkar (816-242-2331) contact.

EXECUTIVE SUMMARY: In an acute delayed neurotoxicity study in hens (MRID# 44996401), disulfoton was acutely administered orally to 18 LSL laying hens at 40 mg/kg bird in a single dose. Fifteen hens were used as controls. Doses were administered in aqueous 2% Cremophor at 5 ml/kg bird. Five to 18 minutes before administration of the disulfoton, atropine was administered s.c. (0.5 ml/kg of 4% atropine sulfate). Directly prior to the administration of the disulfoton, 0.5 ml/kg of 10% atropine sulfate and 10% 2-PAM chloride was injected s.c. The afternoon of day 0, 0.5 ml/kg of 5% atropine sulfate and 5% 2-PAM chloride was injected s.c. and again the morning and afternoon of day 1. Clinical observations were made at least daily. Forced motor activity tests were conducted by forcing the hens to run around a 12-13 m^2 area and rated for coordination, ataxia, and paresis. NTE studies were conducted at 24 and 48 hours on the spinal cords, sciatic nerves and ½ of the brain in each of 3 hens per group. Cholinesterase activity studies were conducted on the other ½ of the brain from each bird in the NTE study at 24 and 48 hours post treatment. The study was conducted at 1.4 times the LD50 for hens.

No typical signs of organophosphate induced delayed neuropathy was seen during the study or on microscopic examination of the treated birds at termination at 3 weeks. No inhibition was seen in the NTE study at 24 hours or 48 hours. Inhibition was low between 4% and 8% and was not considered to be indicative of OPIDP. Cholinesterase activity in the brain was inhibited 83% and 59% at 24 and 48 hours, respectively.

No hens died, but by day 7 there was a decrease in body weight of over 5%. The hens slowly recovered and by the end of 3 weeks, body weight of the treatment group and of the controls did not differ.

Severely uncoordinated gait was observed in all treated birds within 5 minutes of being dosed with atropine and before disulfoton treatment. The report authors attributed this abnormal gait to atropine since it lasted only for the duration of the atropine treatment (2 days). However, the report authors also noted reduced motility in 1-3 birds for 0-1 day, which they attributed to disulfoton treatment. Neither statements are completely supportable because the hens were dosed with atropine and disulfoton during most of this period. However, the temporary uncoordinated gait was followed by no microscopic findings in nerve tissue and no other signs, which supports a conclusion of no demonstrated OPIDP in hens dosed with disulfoton.

Microscopic examination of the test birds showed 3 (25% - 8% in each region, grade 1) lesions in treated birds and 1 (11%, grade 1) in the same control brain regions. Since these lesions were similar to those found in controls from previous studies, they were considered incidental.

The study supports a conclusion the disulfoton does not cause acute delayed neuropathy (OPIDP) in hens.

The study is acceptable for an acute delayed neurotoxicity study (OPPTS# 870.6100) in hens.

870.6200 Acute Neurotoxicity - Rat

CITATION: Sheets, LP and Lake, SG (1993) An acute oral neurotoxicity screening study with technical grade disulfoton (Di-Syston®) in rats Study number 92-412-OB (Miles no. 103992).

Conducted by Miles Inc., Agriculture Division fo Miles Inc. MRID# 42755801.

Executive Summary: In an acute neurotoxicity screening study, disulfoton (97.8% pure) was administered in a single gavage dose to 10 male Sprague-Dawley rats at doses of 0, 0.25, 1.5, or 5.0 mg/kg and to 10 female Sprague-Dawley rats at doses of 0, 0.25, 0.75 or 1.5 mg/kg (MRID# 42755801). These rats were assessed for reactions in functional observational battery (FOB) and motor activity measurements at approximately 90 minutes post-dosing and on days 7 and 14. Cholinesterase determinations (erythrocyte and plasma) were made at 24 hours post-dosing. Six rats/sex/dose were examined for neuropathological lesions.

At 0.75 mg/kg, 4/10 females had muscle fasciculations. At 1.5 mg/kg, males had muscle fasciculations, diarrhea, and sluggishness and females also had tremors, ataxia, oral staining, decreased activity/sluggishness, decreases in motor and locomotor activity (38–49% of control), and a slightly increased duration of nasal staining. One female at 1.5 mg/kg died from cholinergic intoxication on the day of dosing. At 5.0 mg/kg, males also had symptoms similar to those observed in females at 1.5 mg/kg/day, including reduced motor/locomotor activity (36–45% of control). Recovery appeared to be complete in surviving animals by Day 14. **Based on the evidence of neurotoxicity (probably associated with inhibition of cholinesterase) in females at 0.75 mg/kg, the study LOAEL is 0.75 mg/kg and the study NOAEL is 0.25 mg/kg.**

At 0.75 mg/kg in females, cholinesterase activities were inhibited by 53% (erythrocyte) and 30% (plasma) and by 75% (erythrocyte) and 52% (plasma) at 1.5 mg/kg in females. At 5.0 mg/kg in males, cholinesterase activities were inhibited by 21% (erythrocyte) and 25% (plasma). **The LOAEL for inhibition of cholinesterase activity is 0.75 mg/kg and the NOAEL for inhibition of cholinesterase activity is 0.25 mg/kg.**

This study is classified as core-minimum and satisfies the guideline requirement for an acute neurotoxicity screen (81-8).

870.6200 Subchronic Neurotoxicity Screening Battery - Rats

CITATION: L.P. Sheets and B.F. Hamilton (1993) A subchronic dietary neurotoxicity screening study with technical grade disulfoton (Di-Syston®) in Fischer 344 rats. Testing lab.: Miles Inc. Study# 92-472-NS (106332). Date: 9/23/1993. MRID# 42977401. Unpublished study.

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID# 42977401), disulfoton (98.7–99.0% pure) was administered in the diet to 12 male and 12 female Fischer 344 rats at dietary levels of 0, 1, 4, or 16 ppm (0, 0.063, 0.270, and 1.08 mg/kg/day in males and 0, 0.071, 0.315, and 1.31 mg/kg/day in females). Of these 12 rats/sex/dose, 6/sex/dose were used for a neurohistopathological examination at the end of the study.

At 4 ppm, females had muscle fasciculations, urine staining, and increased food consumption (approximately 110% of control). At 16 ppm, both males and females had increased reactivity, perianal staining, tremors, increased defecation, decreased forelimb grip strength (37–86% of control), decreased motor and locomotor activity (39–71% of control), decreased body weight gain (81–83% of control), and corneal opacities. At 16 ppm, males also had muscle fasciculations and appeared sluggish, and one female died due to cholinergic intoxication. **The study LOAEL is 4 ppm (0.315 mg/kg/day) and the study NOAEL is 1 ppm (0.071 mg/kg/day),**

based on clinical signs in females consistent with neurotoxicologic effects of cholinesterase inhibition.

Erythrocyte, plasma, and brain cholinesterase activities were inhibited by 15–23%, 59–80%, and 87–100% in females at 1, 4, and 16 ppm, respectively, and 20–67% and 66–100% in males at 4 and 16 ppm, respectively. Males at 1 ppm had a statistically significant inhibition of erythrocyte cholinesterase at 13 weeks (15% inhibition); other cholinesterase activities in males at 1 ppm were not significantly affected. **The LOAEL for inhibition of cholinesterase activity is 1 ppm and the NOAEL for inhibition of cholinesterase activity is less than 1 ppm.**

This study is classified as core-guideline and satisfies the guideline requirement for a subchronic neurotoxicity screen (82-7).

4.10 Metabolism

Disulfoton is rapidly absorbed and excreted. Three minor oxidative metabolites (Di-Syston sulfone, Di-Syston oxygen analogue sulfoxide, and Di-Syston oxygen analog sulfone) were identified. Sex-related differences in pattern of these metabolites and differences between the single dose and the repeat dose groups were attributed to differences in metabolic rates, rather than different metabolic pathways.

870.7485 Metabolism - Rat

CITATION: Lee, SGK, Hanna, LA, Johnston, K and Ose, K (1985) Excretion and Metabolism of Di-syston® in Rats. Study# 90946. Dated December 9, 1985, September 20, 1988, May 17, 1990 September 26, 1990 and April 29, 1992. Conducted by Mobay Corp. MRID# 42565101.

EXECUTIVE SUMMARY: The aborption, distribution, metabolism and excretion of Di-systion® were studied in groups of male and female Sprague Dawley rats administered a single dose of 0.2 or 1.0 mg/kg Di-syston® - ethylene-1-^{14}C, or a 14-day repeat oral dose of 0.2 mg/kg unlabeled Di-Syston® followed by 0.2 mg/kg [^{14}C]-labeled Di-Syston® on day 15. [^{14}C]-Di-Syston® was rapidly absorbed, distributed, metabolized completely and eliminated in rats under all dosing regimens. Over 95% of the recovered label was excreted in the urine in all groups, and excretion was approximately 90% complete within24 hours of dosing. Less than 2% of the recovered label was in the feces. Bioaccumulation was also not observed, with $\leq$0.3% of the radiolabel recovered in the tissues and $\leq$1% in the carcass.

A major metabolite (43-60% of the radioactivity in the urine) and a minor metabolite (6-20% of the urinary radioactivity) were produced by hydrolysis of oxidative metabolites. These metabolites were identified as sulfonyl [1-(ethylsulfonyl)-2-(methylsulfinyl)ethane] and sulfinyl [1-(ethylsulfinyl)-2-(methylsulfinyl)ethane], respectively. Three minor oxidative metabolites (Di-Syston sulfone, Di-Syston oxygen analogue sulfoxide, and Di-Syston oxygen analog sulfone) were identified. Sex-related differences in pattern of these metabolites and differences between the single dose and the repeat dose groups were attributed to differences in metabolic rates, rather than different metabolic pathways. A metabolic pathway for Di-Syston was proposed.

Study classification: The study is classified as acceptable. The study satisfies the registration requirements under Guideline 85-1 (and Addendum 7) for metabolism in rats. Althjough there were minor deficiencies in the study, they did not affect the overall study results and conclusion (see Reviewer's Discussion, Section E). A metabolite was not fully characterized, however, the testing laboratory inducated that after using different solvents the metabolite co-chromatographed with a oxygenated hydrolytic product of disulfoton, 1-(ethylsulfonyl)-2-(methylsulfinyl)ethane and material at the origin co-chromatographed with 1-(ethylsulfinyl)-2-(methylsulfinyl)ethane.

870.7600 Dermal Absorption - Rats

Dermal absorption was determined to be 36%. Since the total amount absorbed may contribute to the toxicity, total absorption at the mid-dose and after the10 hour skin wash was used for risk assessment (32.7% plus 3.5% residue absorbing after 10 hours).

CITATION: Warren, D.L. (1994) Dermal Absorption of ^{14}C-Disulfoton from the DISYSTON 8 Formulation. Miles, Stilwell, KS. Study No. 94-722-YP. August 30, 1994. MRID 43360201. Unpublished.

EXECUTIVE SUMMARY: In a dermal absorption study (MRID 43360201) ^{14}C-Disulfoton (99.3% a.i., Specific activity 53 mCi/mmol; cold disulfoton 86.5% a.i.) in 150μl emulsion was applied to clipped backs ($\approx$ 15 cm^2 area) of 4 male rats/dose/group at dose levels of 0.85, 8.5, and 85 μg/cm^2 for 1, 4, and 10 hours (MRID# 43360201). At the 10th hour all the skins were washed to terminate the exposure. At the termination of exposure, these animals were kept for an additional 168 hours to determine kinetics of absorption and excretion of the material remaining on/in the skin following washing. Following the application of the material, the rats were placed individually in metabolism cages and total urine and feces collected separately. Following the wash of the application site, the urine and feces were collected in 24 hour aliquots.

Disulfoton is well absorbed and about 31 - 37% and 2.7 - 3.3% of the administered dose was excreted in the urine and feces, respectively. Ten to 30% of the applied dose evaporated during the 10 hours exposure period in all groups. Skin residues as percent of administered dose increased with dose and decreased with time in all groups. The % absorbed increased with time, essentially equal with time. At low dose, the % absorption at 1, 4, and 10 hours was 5.9, 13.7 and 26%; at mid dose it was 4.6, 15.9, and 32.7%; and at high dose 3.6, 12.5 and 25.6%, respectively.

The study is classified as **Acceptable** and satisfies the guideline requirement for dermal penetration study (85-3) in the rat.

4.11 Special/other Studies

Special studies on disulfoton included 3-5 day inhalation, 6-months cholinesterase study and a 3-day dermal studies in rats. The 3-5 day inhalation study showed an acute LC50, and a LOAEL for cholinesterase inhibition. The 6-month cholinesterase study was required because the chronic/carcinogenic study in rats did not show a NOAEL for cholinesterase. The 3-day dermal

study was conducted to aid in the assessment of pesticide handler risk and to determine a NOAEL in the rat for a formulated product. All three studies were used for risk assessment.

870.3100 and Non-Guideline Acute and 3-5 Day Inhalation Study/Rats

CITATION: Anonomus (1978) Acute and 5-Day Inhalation in the rat with disulfoton. Study laboratory: Bayer AG Instit. Study# 7827. Date: 9/27/78.
MRID# 00147754. Unpublished.

Executive Summary: Disulfoton, technical (94.4%) was administered to 20 Wistar rats/sex/group at 0, 34, 48, 51, 64, 78 or 96 μg/L for males and 0, 3.4, 5, 7, 10, 13 or 20 μg/L for females for 4 hours in a nose only experiment (MRID No.: Accession# 258569). The NOAEL for death was 34 μg/L for males and 3.4 μg/L for females. LC50 for males was 60 μg/L with animals dying at $\geq$ 48 μg/L. The LC50 for females was 15 μg/L with animals dying at $\geq$5 μg/L.

In addition, 10 rats/sex were administered disulfoton for 4 hour/day for 5 days by inhalation at 0, 0.5, 1.8 or 9.8 μg/L in a nose only exposure; the following cholinesterase inhibition studies were conducted on 5 rats/sex/group after one of the five 4 hour exposures in the 5 day study. After 1 exposure in males, plasma cholinesterase inhibition ($\geq$17%) occurred at $\geq$1.8 μg/L and erythrocyte cholinesterase inhibition ($\geq$15%) occurred at 9.8 μg/L. After 1 exposure in females, plasma cholinesterase inhibition ($\geq$40%) occurred at $\geq$1.8 μg/L and erythrocyte cholinesterase inhibition ($\geq$23%) occurred at $\geq$9.8 μg/L.

After 3 to 5 exposures in males, plasma cholinesterase inhibition was reduced ($\geq$40%) and erythrocyte cholinesterase inhibition ($\geq$16%) at $\geq$1.8μg/L. After 3 to 5 exposures in females, plasma cholinesterase inhibition was reduced ($\geq$31%) at $\geq$0.5 μg/L and erythrocyte cholinesterase inhibition was reduced ($\geq$17%) at $\geq$1.8 μg/L. No deaths occurred after one 4 hours exposure at 9.8 μg/L in either males or females, however, deaths occurred in females after the 3rd exposure at 9.8 μg/L.

The acute inhalation NOAEL/LOAEL for males and females are 0.0005/0.0018 mg/L based on increased plasma cholinesterase inhibition and NOAEL/LOAEL of 0.0018/0.0098 mg/L for males and females based on increased erythrocyte cholinesterase inhibition after 1 exposure.

After 3 to 5 exposures, males showed NOAEL/LOAEL of 0.0005/0.0018 mg/L based on increased plasma and erythrocyte cholinesterase inhibition. Females showed NOAEL/LOAEL of <0.0005/0.0005 mg/L based on increased plasma cholinesterase inhibition after 3 to 5 exposures and the NOAEL/LOAEL are 0.0005/0.0018 mg/L based on increased erythrocyte cholinesterase after 3 to 5 exposures.

The study is acceptable under Guideline 81-3 for acute inhalation in rats and is acceptable for a NG 3-5-day inhalation study in rats.

Non-Guideline Special 6-Month Cholinesterase Study

CITATION: W.R. Christenson, B.S. Wahle (1993) Technical grade disulfoton (Di-Syston®): A

special 6-month feeding study to determine a cholinesterase no-observed-effect level in the rat. Study# 91-972-IR, (12/3/1993), conducted at Miles Inc., Agricultural Division, Toxicology Stilwell, Kansas for Miles Inc., Agricultural Division, Kansas City, Missouri. MRID No.: 43058401. Unpublished Report.

EXECUTIVE SUMMARY: In a 6-month study designed to establish a NOAEL and LOAEL for cholinesterase inhibition, technical grade disulfoton (98-99% pure) was administered in the diet to 35 male and female Fischer 344 rats for up to 6 months at levels of 0, 0.25, 0.5 or 1 ppm (approximate doses of 0, 0.02, 0.03 or 0.06 mg/kg/day for males and 0, 0.02, 0.03 or 0.07 mg/kg/day for females)(MRID# 43058401). At the end of 2, 4 and 6 months, 10 rats/sex/dose were taken for blood and brain cholinesterase assays.

Statistically significant inhibition of cholinesterase activity was observed in erythrocytes in females at all doses (3-14% inhibition, 11-17% inhibition, and 23-29% inhibition at 0.24, 0.5, and 1.0 ppm, respectively. In addition, at 1.0 ppm, males had decreased erythrocyte cholinesterase activity (10-16% inhibition) and females had decreased plasma (8-17% inhibition) and brain (7-13% inhibition) cholinesterase activities. However, biologically significant and statistically significant inhibition of cholinesterase activity was observed only in the plasma, erythrocytes and brain of females at 1.0 ppm. No biologically significant inhibition of cholinesterase activity was observed in males.

The LOAEL for inhibition of cholinesterase activity was 1.0 ppm is based on a 23-29% inhibition of erythrocyte, 12-17% inhibition of plasma and 13% inhibition of brain cholinesterase in females. The NOAEL is 0.5 ppm (0.03 mg/kg/day). No biological meaningful cholinesterase inhibition was observed in males at any dose level.

Body weight, food consumption, and clinical signs were also monitored, but showed no treatment related effects. **Based on these few parameters, no systemic effects were observed at any dose level and the NOAEL for systemic toxicity was 1.0 ppm (0.06 mg/kg/day for males and 0.07 mg/kg/day for females).**

Core classification: The special non-guideline study is acceptable for the requested 6-months cholinesterase study in rats.

Non Guideline 3-Day Dermal study - Rats

CITATION: Croutch, CR and Sheets, LP (2000). Repeat-Exposure (3-Day) Dermal Toxicity Study with 1% G Di-Syston®) in Rats. Testing Laboratory name Bayer Corp., Stilwell, KA. Laboratory report number: 109956, Study#00-S22-BS. October 16, 2000. MRID# 45239602. Unpublished

SPONSOR: Bayer Corp., Stilwell KA

EXECUTIVE SUMMARY: In a 3-day dermal rat study (MRID# 45239602) disulfoton, granular, 1% a.i. (1% G Di-Syston®)) was administered dermally to 5 Wistar (Crl:WI(HAN)BR) rats/sex/dose at 0, 50, 100, 200 or 500 mg/kg/day (equivalent to 0, 0.5, 1.0, 2.0 or 5.0 mg a.i./kg/day). Plasma and erythrocyte cholinesterase was measured at 24 hours after the first and day

3 dose. Brain cholinesterase was measured at termination on day 4. Test material was ground and applied to plastic backed gauze, moistened with water, applied to the shave the test site (about 10% of the body surface), then secured with a bandage. The animals were exposed dermally for 6 hour per day with washing at the end of the exposure period.

No clinical signs were noted or body weight decrement. No other signs of toxicity were noted, but the study was designed to determine cholinestersase depression only. After 1 day of dosing, the NOAEL in males was 200 mg/kg and the LOAEL was 500 mg/kg based on biologically significant 31% erythrocyte cholinesterase inhibition which was not statistically significant. After 1 day of dosing the NOAEL in females was 100 mg/kg and the LOAEL was 200 mg/kg based on biologically significantly increased inhibition of plasma cholinesterase (36%). After 3-days of dermal dosing the NOAEL in males was 100 mg/kg/day and LOAEL was 200 mg/kg/day based on a increase in brain cholinesterase inhibition of 21% (statistically significant). After 3-day of dosing the NOAEL in females was 50 mg/kg/day and the LOAEL was 100 mg/kg/day based on statistically significant plasma and brain cholinesterase inhibition of 37% and 18%, respectively.

The overall NOAEL of 100 mg/kg/day (equivant to 1.0 mg a.i./kg) with a LOAEL of 200 mg/kg/day (equivalent to 2.0 mg a.i./kg) based female plasma cholinesterase deprssion for 1 day of dosing. After 3 days of dosing the NOAEL was 50 mg/kg/day (equivalent to 0.50 mg a.i./kg/day) with a LOAEL of 100 mg/kg/day (equivalent to 1.0 mg a.i./kg/day) based on depressed plasma and brain cholinesterase in females.

The study is acceptable for a (NG) 1-day or 3-day dermal study in the rat.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 8.2 for Endpoint Selection Table.

5.2 Dermal Absorption

The test material was applied to the backs of rats at 0.85, 8.5, and 85 $\mu g/cm^2$ (approximately 0.051, 0.51 and 5.1 mg/kg). The percent of absorbed dose after the skin wash 10 hours post-application was approximately 36% at the mid-dose (MRID# 43360201).

Dermal Aborption Factor: 36%

The HIARC indicated that dermal absorption of 36%, obtained after 10 hours exposure at a concentration of 8.5 $\mu g/cm^2$ (0.51 mg/kg), should be used for correcting oral dosing to dermal dosing. The HIARC concurred with the TES Committee on this approach for the use of the dermal absorption factor. HIARC deviated from the standard practice of using the 10-hour dermal absorption value from the lowest application rate in this case because of the lack of a coherent pattern of absorption normally observed in dermal absorption studies. In most cases, the lowest application rate results in the highest dermal absorption rate, with declining absorption at higher applications. This is assumed to reflect overloading of the site of application. In as much as there was no dose-related pattern to the percent of disulfoton absorbed, HIARC elected to use the 36% absorption rate to reduce the likelihood of underestimation.

5.3 Classification of Carcinogenic Potential

The HED RfD/Peer Review classified disulfoton as a Group E Chemical-Not Classifiable to Carcinogenicity based on the lack of evidence of carcinogenicity study in mice and rats at dose levels adequate to test for carcinogenicity.

5.3.1 Quantification of Carcinogenic Potential

Not applicable

6.0 FQPA Considerations

Adequacy of Toxicology Database

The toxicology database is adequate for FQPA considerations. On January 19, 2000, the HIARC reviewed the submitted acute delayed neurotoxicity study with disulfoton in the hen which was previously identified as data gap. The HIARC determined that this study is acceptable and therefore, the toxicology database is now adequate according to the standard Subdivision F and/or OPPTS Series 870 Guideline requirements for a food-use chemical.

a. Evaluation of Neurotoxicity

The repeat acute delayed neurotoxicity study in hens (required by HIARC during the Hazard Assessment of the Organophosphates; May 12-14, 1998) has been received and reviewed, and found to be negative for organophosphate induced delayed neuropathy (OPIDP).

There are also acute and subchronic neurotoxicity studies with disulfoton in rats. The acute study shows neurotoxicity in the form of tremors and muscle twitching and decreased motor activity, but no neuropathology (MRID No. 42755801). The subchronic study shows similar neurotoxicity and nominal increased incidence of neuropathy in the form of nerve fiber degeneration in the optic nerve and thoracic spinal cord at the highest dose tested (MRID No. 42977401). On January 19, 2000, the HIARC concluded that the differences in the effects observed between the high dose animals and control animals in the subchronic neurotoxicity study in rats, were not sufficiently great to indicate that a treatment-related effect had occurred.

b. Developmental Toxicity

In a prenatal developmental toxicity study in rats, developmental toxicity occurred only in the presence of maternal toxicity (MRID No. 00129458).

In a prenatal developmental toxicity study in rabbits, there was no evidence of developmental toxicity even at the highest dose tested (MRID No. 00147886).

c. Reproductive Toxicity

In a two-generation reproduction study rats, the effects in pups were caused by maternal toxicity and not the direct toxicity of disulfoton on pups (MRID No. 44440801).

6.1 Special Sensitivity to Infants and Children

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to disulfoton. There was no indication of increased susceptibility in the offspring as compared to parental animals in the two generation reproduction study. In these studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of maternal/parental toxicity.

6.2 Recommendation for a Developmental Neurotoxicity Study

On January 19, 2000, the HIARC concluded that although a developmental neurotoxicity study (DNT) with disulfoton in rats has been required as part of the Data-Call-In for select organophosphates, this requirement was not, however, 'triggered' by a special concern for the developing fetuses or young which are generally used for requiring a DNT study and an FQPA safety factor (e.g.: neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring).

7.0 RERERENCES

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and

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00147754 CITATION: Anonomus (1978) Acute and 5-Day Inhalation in the rat with disulfoton. Study laboratory: Bayer AG Instit. Study# 7827. Date: 9/27/78. MRID# 00147754. Unpublished.

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8.0 APPENDICES

Tables for Use in Risk Assessement

8.1 Toxicity Profile Summary Tables

8.1.1 Acute Toxicity Data Table on disulfoton

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral	00139595,Doc# 003958,p41	LD_{50} = M: 6.2 mg/kg; F:1.9 mg/kg	I
870.1200	Acute Dermal	Acc# 07793, Doc# 03958,p71 & 004223,p24	LD_{50} = M: 15.9 mg/kg; F: 3.6 mg/kg	I
870.1300	Acute Inhalation	00147754, Doc# 05789	LC_{50} = M: 0.06 mg/L; F: 0.015 mg/L	I
870.2400	Primary Eye Irritation	Data requirement waived. Doc# 03958,p12; 004223,p14	Defaults to most severe category	
870.2500	Primary Skin Irritation	Data requirement waived. Doc# 03958,p12;004223.p14	Defaults to most severe category	
870.2600	Dermal Sensitization	Data requirement waived. Doc# 03958, p12	Defaults to most severe category	
870.6100	Acute Delayed Neurotoxicity/Hen	44996401, Doc# 013957	Negative for OPIDP and NTE effects	
870.6200	Acute Neurotoxicity/Rat	42755801	Reversible neurotoxic signs with cholinesterase inhibition NOAEL = 0.25 mg/kg LOAEL = 0.75 mg/kg	

8.1.2 Subchronic, Chronic and other Toxicity Tables

Table A and B are respectively, the Toxicity Profile for Disulfoton Technical and a 1% granular formulation

used for Short-Term occupational/residential exposure.

Table A: Toxicity Profile for Disulfoton, Technical

Guideline No./Type of Study	MRID No. (year)/Classification/Doses	Results
Non-guideline Acute Inhalation - Rat (1 day in a 3-5 day exposure study)	00147754 (1978) Acceptable 0, 0.0005, 0.0018 or 0.0098 mg/mL	NOAEL (ChE Inhibition) = 0.0005 mg/L LOAEL (ChE Inhibition) = 0.0018 mg/L
21-Day Dermal Toxicity-Rabbit	00162338 (1986) Acceptable 0, 0.4, 1.6 or 6.5 mg/kg/day	NOAEL (Systemic) = 1.6 mg/kg/day LOAEL (Systemic) = 6.5 mg/kg/day NOAEL (ChE Inhibition) = 0.4 mg/kg/day LOAEL (ChE Inhibition) = 1.6 mg/kg/day
21-Day Dermal Toxicity-Rabbit	45239601 (1988) Acceptable 0, 0.8, 1.0, or 3.0 mg/kg/day	NOAEL (Systemic) = 1.0 mg/kg/day LOAEL (Systemic) = 3.0 mg/kg/day NOAEL (ChE Inhibition) = 0.8 mg/kg/day LOAEL (ChE Inhibition) = 1.0 mg/kg/day
870.3465 Subchronic Inhalation - Rat	41224301 (1989) Acceptable 0, 0.000018, 0.00016, or 0.0014 mg/mL	NOAEL = (ChE Inhibition) = 0.00016 mg/L LOAEL = (ChE Inhibition) = 0.0014 mg/L
Subchronic-Feeding-Rat		Data waived because an adequate chronic study was available
Subchronic-Feeding-Dog		Data waived because an adequate chronic dog study was available
870.4100 Chronic-Feeding-Dog (1-year)	44248002 (1997) Acceptable Males- 0, 0.015, 0.121 or 0.321 mg/kg/day; Females- 0, 0.013, 0.094 or 0.283 mg/kg/day	NOAEL (ChE Inhibition)=0.013 mg/kg/day LOAEL (ChE Inhibition)= 0.094 mg/kg/day

870.4100 Chronic-Feeding-Dog (1-year)	00073348 (1975) Acceptable 0, 0.0125, 0.025 or 0.05/0.125/0.2 mg/kg/day	NOAEL = (ChE Inhibition) = 0.025 mg/kg/day LOAEL (ChE Inhibition) = 0.05 mg/kg/day
870.4300 Chronic toxicity/Carcinogenicity-Rat	00146873; 41850001; 41850002 (1985) Acceptable 0, 0.04, 0.165 or 0.650 mg/kg/day	NOAEL (systemic) = 0.04 mg/kg/day LOAEL (systemic) = 0.165 mg/kg/day (HDT) NOAEL (ChE Inhibition) = Not demonstrated LOAEL (ChE Inhibition) = 0.04 mg/kg/day (LDT) **No evidence of carcinogenicity**
870.4300 Chronic toxicity/Carcinogenicity-Rat	00069966 (1976) Unacceptable Males- 0, 0.0215/0.19, 0.456 or 0.0893 mg/kg/day; Females- 0, 0.0267/0.196, 0.0419 or 0.103 mg/kg/day	NOAEL (ChE inhibition) = 0.042 mg/kg/day LOAEL (ChE inhibition) = 0.103 mg/kg/day
870.4200 Carcinogenicity - Mouse	00129456; 00139598 (1983) Acceptable 0, 0.15, 0.6 or 2.4 mg/kg/day	NOAEL (ChE Inhibition) = 0.6 mg/kg/day LOAEL (ChE Inhibition) = 2.4 mg/kg/day (HDT) **No evidence of carcinogenicity**
870.3700 Developmental Toxicity-Rat	00129458 (1983) Acceptable 0, 0.1, 0.3 or 1.0 mg/kg/day	Maternal NOAEL = 0.1 mg/kg/day LOAEL = 0.3 mg/kg/day Developmental NOAEL = 0.3 mg/kg/day LOAEL = 1.0 mg/kg/day
870.3700 Developmental Toxicity-Rabbit	00147886 (1982) Acceptable 0, 0.3, 1.0 or 3.0 mg/kg/day	Maternal NOAEL = 1.0 mg/kg/day LOAEL = 1.5 mg/kg/day Developmental NOAEL= >3.0 mg/kg/day LOAEL = >3.0 mg/kg/day

870.3800 Reproductive Toxicity - Rat	44440801 (1997) Acceptable 0, 0.25, 0.10 or 0.45	Parental/Systemic: NOAEL = Not established LOAEL = 0.025 mg/kg/day (LDT) Offspring NOAEL = 0.10 mg/kg/day LOAEL = 0.45 mg/kg/day (HDT)
870.3800 Reproductive Toxicity - Rat	00157511 (1986) Acceptable 0, 0.04, 0.12 or 0.36 mg/kg/day	Parental/Systemic: NOAEL = 0.04 mg/kg/day LOAEL = 0.12 mg/kg/day Offspring NOAEL = 0.04 mg/kg/day LOAEL = 0.12 mg/kg/day
870.5100 Gene Mutation - *Salmonella*	Acc# 00028625, Doc# 003958, 012190 (1979) Acceptable	Non-mutagenic (±) activation.
870.5300 Gene Mutation - HGPRT	40638401 (1988) Unacceptable 0.001-10.0 μL/mL	Assumed positive because tested at partially soluble conditions. Response was greater (-) activation.
870.5395 Mouse micronucleus Chromosomal aberrations	43615701, Doc# 012292 (1995) Acceptable 8 mg/kg	Non-mutagenic (±) activation.
870.5500 Bacterial DNA Damage/Repair	00146894, Acc# 072293, Doc# 004698 (1983) Acceptable 625-10000μg/plate	Non-mutagenic (±) activation
870.5577 Mitotic Recombination	Acc# 00028625, Doc# 003958, 012190 (1979) Acceptable	Non-mutagenic (±) activation
870.5900 Sister Chromatid Exchange	40495001 (1987) Acceptable 0.013 - 0.2 μL/mL	Mutagenic (-) activation, but non-mutagenic (+) activation.
870.5900 Sister Chromatid Exchange	Acc# 072293, Doc# 0044223 Acceptable up to 80 μg/mL	Non-mutagenic (±) activation

870.5550 Unscheduled DNA Synthesis	Acc#028625, Doc# 003958 (1979), Acceptable	Mutagenic (-) activation, but non-mutagenic (+) activation
870.5300 Mouse Lymphoma	EPA-600/1-84-003	Mutagenic (-) activation, but non-mutagenic (+) activation.
870.5395 Mouse Micronucleus	EPA-600/1-84-003	Non-mutagenic.
870.5900 Sister Chromatid Exchange	EPA-600/1-84-003	Weakly mutagenic (+) activation, but non-mutagenic (-) activation
870.6100 Acute Delayed Neurotoxicity-Hen	44996401 (1999) Acceptable 40 mg/kg	No demonstrated acute delayed neuropathy (OPIDP)
870.6200 Acute Neurotoxicity - Rat	42755801 (1993) Acceptable Males-0, 0.25, 1.5 or 5.0 mg/kg; Females-0, 0.25, 0.75 or 1.5 mg/kg	NOAEL (ChE Inhibition) = 0.25 mg/kg LOAEL (ChE Inhibition & clinical signs) = 0.75 mg/kg/day
870.6200 Subchronic Neurotoxicity - Rat	42977401 (1993) Acceptable Males: 0, 0.063, 0.270 or 1.08 mg/kg/day; Females 0, 0.071, 0.315 or 1.31 mg/kg/day	NOAEL (Clinical signs) = 0.071 mg/kg/day LOAEL (Clinical signs) = 0.315 mg/kg/day (HDT) NOAEL (ChE Inhibition)= Not established. LOAEL (ChE Inhibition)= <0.071mg/kg/day (LDT)
870.7485 Metabolism-Rat	42565101 (1985) Acceptable 0.2 or 1.0 mg/kg/day	Greater than 90 percent of the administered radioactivity was metabolized completely and eliminated within 24 hours. About 95 percent of the radiolabel was recovered in the urine, <2 percent in the feces, <0.3 percent in tissues and <1 percent in the carcass. No bioaccummulation was noted. Sex related differences were attributed to different metabolic rates rather than different profiles. The (toxicologically inactive) major and minor metabolites were produced by hydrolysis of oxygen metabolites.

870.7600 Dermal Absorption - Rats	43360201 (1994) Acceptable 0.85, 8.5 or 85 $\mu g/cm^2$	Dermal absorption is considered to be 36 percent after skin wash at 10 hours
Non-guideline Subacute Inhalation - Rat (3-5 day exposure)	00147754 (1978) Acceptable 0, 0.0005, 0.0018 or 0.0098 mg/L	NOAEL (ChE Inhibition) = Not established LOAEL (ChE Inhibition) = 0.0005 mg/L
Non-guideline Special 6-Month Cholinesterase - Rat - (Non-guideline study)	43058401 (1993) Acceptable Males- 0, 0.02, 0.03 or 0.6 mg/kg/day; females- 0, 0.02, 0.03, or 0.07 mg/kg/day	NOAEL (ChE Inhibition) = 0.03 mg/kg/day LOAEL (ChE Inhibition) = 0.07 mg/kg/day
Table B: Summary data on a 1% granular formulation used for occupational/residential exposure		
Non-guideline 3-Day Dermal Toxicity - Rat 1% granular formulation Non-guideline study)	45239602 (2000) Acceptable 0, 0.5, 1.0, 2.0 or 5.0 mg a.i./kg/day	NOAEL = 1.0 mg a.i./kg/day LOAEL (ChE Inhibition) = 2.0 mg a.i. /kg/day

8.2 Summary of Toxicological Dose and Endpoints for Disulfoton for Use in Human Risk Assessment.[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, females 13-50 years of age	None		
Acute Dietary general population including infants and children	NOAEL = 0.25 mg/kg UF = 100 Acute RfD = 0.0025 mg/kg	FQPA SF = 1 aPAD = Acute RfD / FQPA SF = 0.0025 mg/kg	Acute Neurotoxicity - Rat LOAEL = 0.75 mg/kg based on neurotoxic signs and plasma, erythrocyte cholinesterase inhibition in female rats.
Chronic Dietary all populations	NOAEL = 0.013 mg/kg/day UF = 100 cRfD = 0.00013 mg/kg/day	FQPA SF = 1 cPAD = cRfD / FQPA SF = 0.00013 mg/kg/day	Chronic Feeding - Dog LOAEL = 0.094 mg/kg/day based on depressed plasma, erythrocyte and corneal cholinesterase levels in both sexes and depressed brain and retinal cholinesterase levels in females.
Short-Term oral (1-7 days)	NOAEL = 0.25 mg/kg UF = 100 Acute RfD = 0.0025 mg/kg	FQPA SF = 1 aPAD = Acute RfD / FQPA SF = 0.0025 mg/kg	Acute Neurotoxicity - Rat LOAEL = 0.75 mg/kg based on neurotoxic signs and plasma, erythrocyte cholinesterase inhibition in female rats.
Intermediate-Term Oral (1 week to several months)	Oral study NOAEL = 0.03 mg/kg/day	LOC or MOE = 100 (Residential includes the FQPA SF)	Special 6-months Cholinesterase study in Rats LOAEL = 0.07 mg/kg/day based on plasma, erythrocyte and brain cholinesterase inhibition in females.
Short-Term Dermal (1-7 days) (Occupational/ residential)	Dermal study NOAEL = 0.5 mg/kg/day UF = 100	LOC or MOE = 100 (Occupational) LOC or MOE = 100 (Residential, includes FQPA SF)	3-day Dermal Study in Rats LOAEL = 1.0 mg/kg/day based plasma and brain cholinesterase inhibition in females.

Intermediate-Term Dermal (1 week to several months) (Occupational/ residential)	Oral study NOAEL = 0.03 mg/kg/day Dermal absorption rate = 36%	LOC or MOE = 100 (Occupational) LOC or MOE = 100 (Residential, includes FQPA SF)	Special 6-months Cholinesterase study in Rats LOAEL = 0.07 mg/kg/day based on plasma, erythrocyte and brain cholinesterase inhibition in females.
Long-Term Dermal (Several months to life time) (Occupational/residential)	Oral study NOAEL = 0.013 mg/kg/day Dermal absorption rate = 36%	LOC or MOE = 100 (Occupational) LOC or MOE = 100 (Residential, includes FQPA SF)	Chronic feeding study in dogs LOAEL = 0.094 mg/kg/day based on depressed plasma, erythrocyte and corneal cholinesterase levels in both sexes and depressed brain and retinal cholinesterase levels in females.
Inhalation (all time periods)	Inhalation study NOAEL = 0.00016 mg/mL	LOC or MOE = 100 (Occupational) LOC or MOE = 100 (Residential, includes FQPA SF)	90-day Inhalation study in Rats LOAEL = 0.0014 mg/mL based on plasma, erythrocyte and brain cholinesterase inhibition in males and females.
Cancer (oral)	Cancer classification: E, not likely to be a human carcinogen	None	No treatment related tumors in the rat or the mouse in adequate studies

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD population adjusted dose (a= acute, c = chronic), RfD = reference dose, LOC = level of concern, MOE = margin of ex.posure

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Toxicology Branch:	RRB2